National Library of Medicine

FOUNDED 1836

Bethesda, Md.

U. S. Department of Health, Education, and Welfare

PUBLIC HEALTH SERVICE

DIVISION of BIOLOGICS STANDARDS

2-

dbs

he DIVISION of BIOLOGICS STANDARDS

Fifty-seventh Congress of the United States of America;

At the First Session,

Begun and held at the City of Washington on Monday, the second day of December, one thousand nine hundred and one.

AN ACT

To regulate the sale of viruses, serums, toxins, and analogous products in the District of Columbia, to regulate interstate traffic in said articles, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That from and after six months after the promulgation of the regulations authorized by section four of this Act no person shall sell, barter, or exchange, or offer for sale, barter, or exchange in the District of Columbia, or send, carry, or bring for sale, barter, or exchange from any State, Territory, or the District of Columbia into any State, Territory, or the District of Columbia, or from any foreign country into the United States, or from the United States into any foreign country, any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention and cure of diseases of man, unless (a) such virus, serum, toxin, antitoxin, or product has been propagated and prepared at an establishment holding an unsuspended and unrevoked license, issued by the Secretary of the Treasury as hereinafter authorized, to propagate and prepare such virus, serum, toxin, antitoxin, or product for sale in the District of Columbia, or for sending, bringing, or carrying from place to place aforesaid; nor (b) unless each package of such virus, serum, toxin, antitoxin, or product is plainly marked with the proper name of the article contained therein, the name, address, and license number of the manufacturer, and the date beyond which the contents can not be expected beyond reasonable doubt to yield their specific resu[illegible] Provided, That the suspension [illegible]

[illegible] That [illegible] consistent with the provisions of this Act be, and the same are hereby, repealed.

Speaker of the House of Representatives.

President of the Senate pro tempore.

Approved,
July 1, 1902.

Theodore Roosevelt

U.S. National Institutes of Health. Division of Biologics Standards.

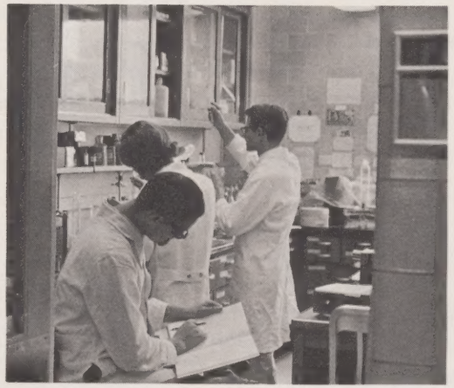
dbs

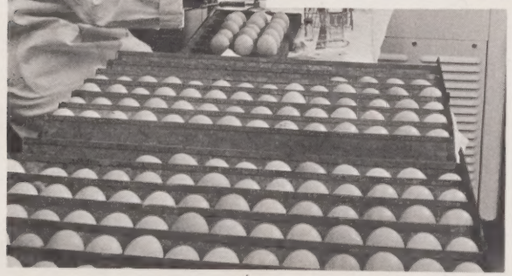
the DIVISION of BIOLOGICS STANDARDS

"To apply our present knowledge to the improvement of biologics now on the market, to find better ways of producing and testing these biologics, and to help in the development of new immunizing agents against the infectious diseases that, so far, have baffled science—these are the ultimate aims of those concerned with the control of biologics."

Director,
Division of Biologics Standards

For sale by the Superintendent of Documents, U.S. Government Printing Office
Washington, D.C. 20402 - Price 15 cents





DBS staff works in two modern, interconnected buildings on the campus of the National Institutes of Health, at Bethesda, Maryland. The staff of approximately 300 includes more than 100 professional members—physicians, biochemists, virologists, biologists, and immunologists. Although the research interests of the Division cut across many disciplines, the work is organized into seven laboratories: Control Activities, Bacterial Products, Biophysics and Biochemistry, Blood and Blood Products, Pathology, Viral Immunology, and Virology and Rickettsiology.

BIOLOGICS REGULATION

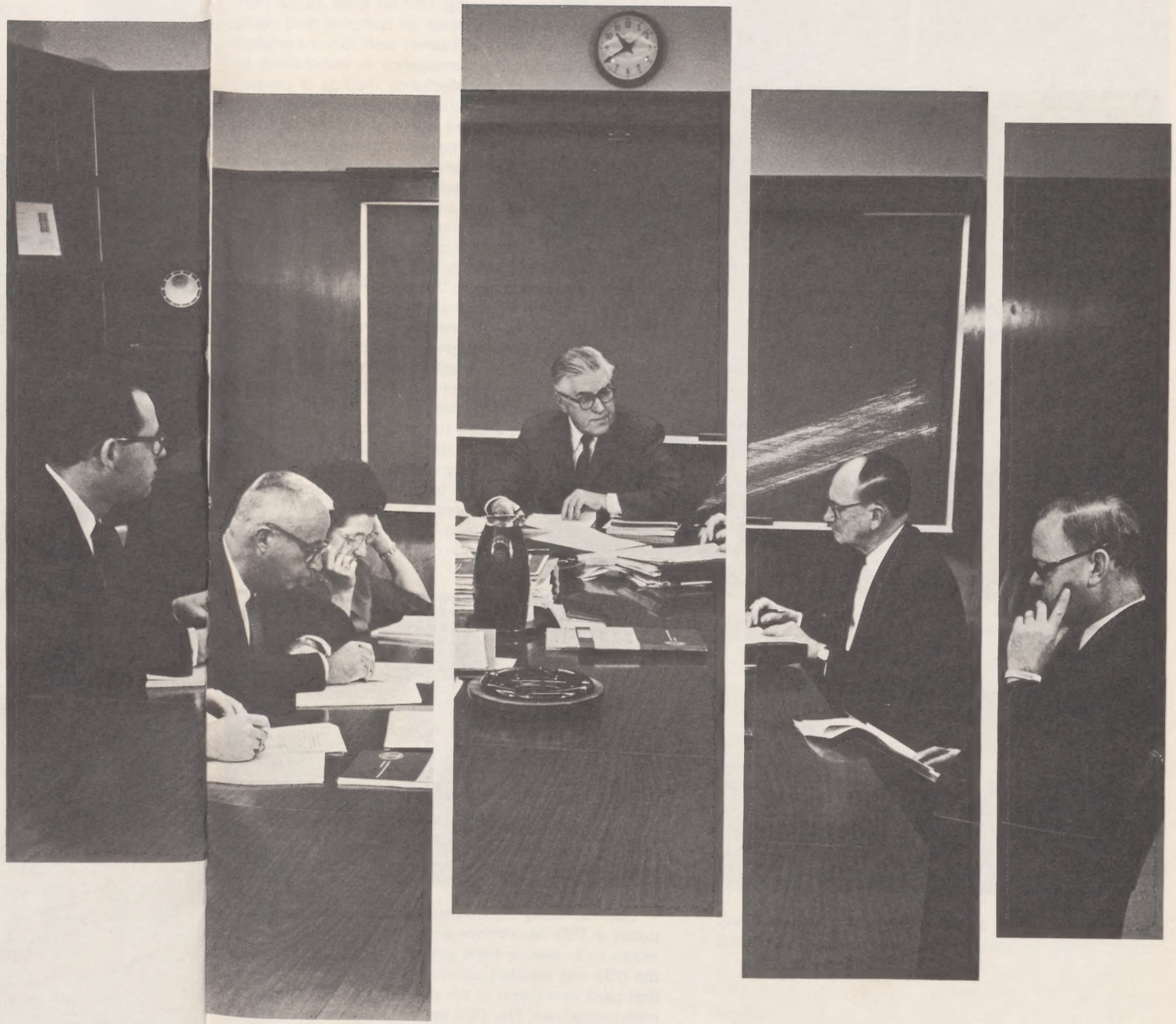
The DBS is responsible for establishing and maintaining standards of quality and safety of all biological products that come within the jurisdiction of the Public Health Service. These products include all vaccines, antitoxins, therapeutic serums, allergenic products, and human blood for transfusion, as well as products prepared from human blood.

Because many of these products are derived from living organisms, such as bacteria and viruses, and all by their nature are either potentially dangerous or ineffective if improperly prepared and tested, close surveillance of production is essential. The development of realistic standards for these products and the exercise of proper control over them is effectively backed by a flexible research program.

The standards for the production and testing of biological products are set forth in regulations prescribed by DBS. As scientific knowledge advances, revisions are made in the regulations.

Following determination by the DBS that the prescribed standards for safety, purity, and potency have been met, licenses for the manufacturing establishment and for the product are issued by the Department of Health, Education, and Welfare upon recommendation of the Surgeon General of the Public Health Service.

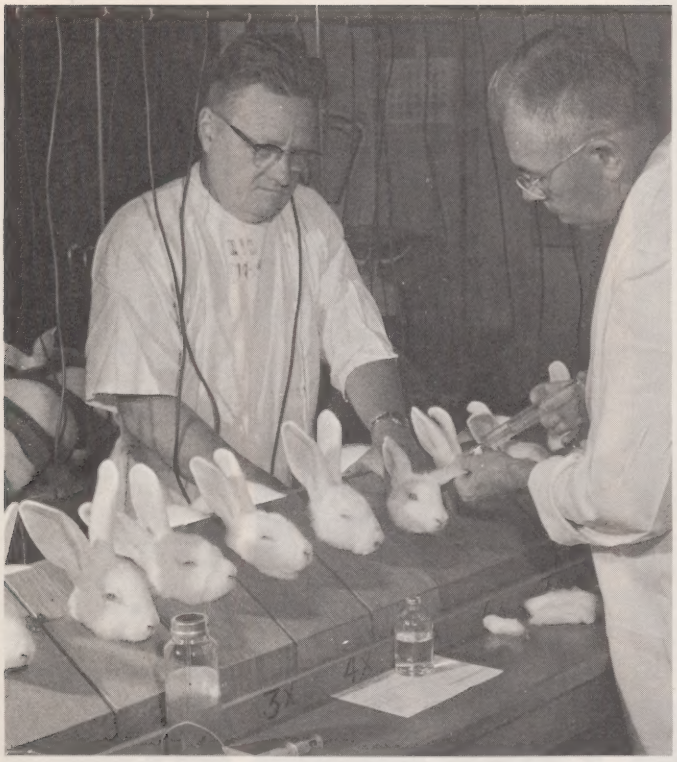
Food and Drug Administration regulations require the monitoring of clinical trials of all investigational drugs. The Division therefore maintains surveillance of all experimental biological materials under study for potential commercial use.



CONTROL TESTING

The safety, purity, and potency of all biologics must be established before licensing. Control tests range from relatively simple sterility tests to complex and costly potency determinations and safety tests. Once a product is licensed, continuing surveillance is maintained by inspection, review of manufacturing records of production and testing, and by testing samples of the product.

Animals play an important role in control testing. Mice, guinea pigs, rabbits, and monkeys provide a variety of responses by which the safety, purity, and potency of these products can be evaluated.



Safety tests in animals are performed to ensure the relative freedom from harmful effects to the recipient of the product. The guinea pig is used in safety tests for all vaccines, toxins, and toxoids.

Closely allied to safety is the requirement of ***purity,*** or freedom from extraneous matter in the finished product. For example, to ensure freedom from fever-producing substances of bacterial origin for antitoxins, plasma, and other blood derivatives, a test dose of the product is injected into the ear veins of rabbits. Elevation of body temperature indicates the presence of impurities.

To determine ***potency*** – the specific ability of a biologic to effect a specific result – a number of specialized tests are involved, including animal tests. In diphtheria and tetanus toxoid potency tests, the animal may serve to measure immune response to the product. The potency of typhoid vaccine is measured by immunizing mice; potency of smallpox vaccine is tested by the rabbit skin test.

Approximately 35,000 control tests are conducted annually in DBS laboratories on samples of manufacturers' products to ensure their safety, purity, and potency. If the DBS test results confirm those of the manufacturer, that particular batch of the product can be released for commercial use. The DBS tests serve as a basis for the annual release of some 4,000 production lots.

Some 180,000 mice, 3,500 rabbits, 2,000 monkeys, and 8,600 guinea pigs are used annually for control tests.

VIRAL / BACTERIAL RESEARCH

The availability and use of viral and bacterial antigens has for many years protected millions of people against infectious diseases. Smallpox vaccination and the multiple antigen (diphtheria and tetanus toxoids and pertussis vaccine) are routinely given in this country to children of pre-school age. Travelers in areas of the world where typhoid fever, yellow fever, cholera, and typhus are prevalent are immunized against these diseases.

Despite the long-time use of these immunizing agents, there is always need for their improvement in the light of current scientific knowledge. DBS investigators continue to devise better methods of testing for viral, bacterial, and rickettsial antigens.

It was, however, the advent of tissue-culture-produced virus vaccines which revolutionized biologics production. The first of these was the inactivated Salk polio vaccine, licensed in 1955. The development of the live, oral, Sabin poliovirus vaccine presented DBS with a new technical challenge. The monkey neurovirulence tests required for this vaccine involved extensive studies. More than 150 neurovirulence tests were made in more than 7,500 monkeys during 1959-1961. These studies led to the establishment of a standardized test system which assured the safety of the Sabin polio vaccine. Research, testing, and the development of standards in connection with measles vaccine represented another major concern for DBS, beginning soon after measles (rubeola) virus was isolated by Dr. John Enders in 1954 and continuing until the vaccine was licensed in 1963.

Research is also directed toward the formulation of standards for new products. Advances in virology have led rapidly toward the development of viral vaccines for mumps, German measles, and some of the respiratory diseases. Studies are also conducted on diseases for which etiologic agents have not yet been isolated. Of increasing importance is the intensive study of the role that viruses may play in human malignancies.

TUMOR VIRUSES

Many if not all animals harbor latent viruses, some of which may have a tumor-producing or "oncogenic" potential. This is of concern in biologics control since most virus vaccines are produced in animals or chick embryo tissue cultures or in embryonated eggs.

One such virus, SV-40, found to be present in monkey kidney tissue culture, can cause tumors in hamsters. Another, avian leukosis virus, causes tumors in chickens. Since the role of these viruses in relation to human disease is unknown, the only position the Public Health Service can take is to require their exclusion from all licensed vaccines.

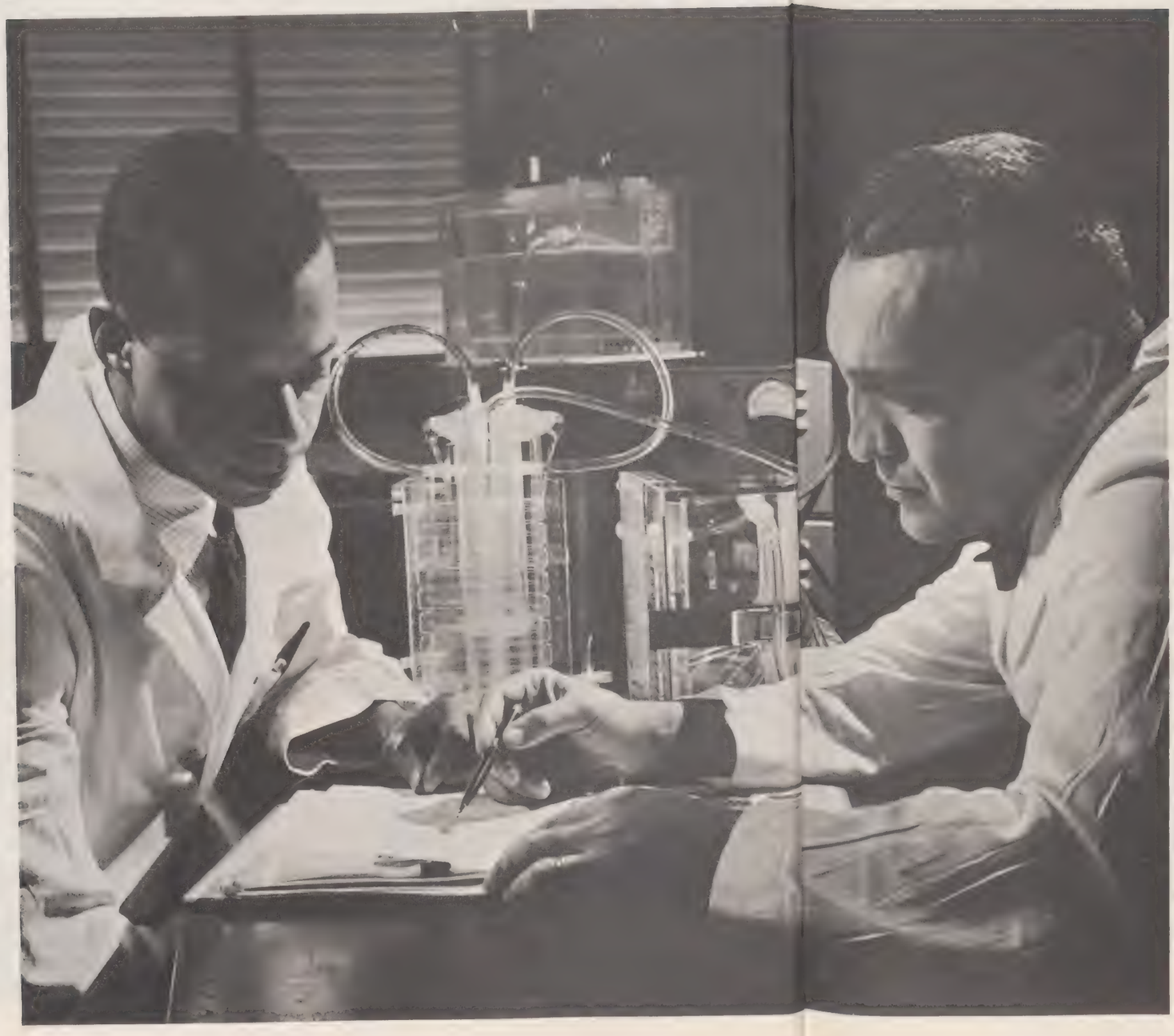
Future vaccines will undoubtedly be produced in other tissue culture systems; therefore, DBS scientists are developing methods and special techniques to reveal potentially oncogenic viruses. These include animal inoculation, electron microscopy, and histologic evaluation of tumor cells. For example, newborn hamsters have been found to be particularly susceptible to tumor induction by animal viruses and are used in demonstrating the tumor-producing capability of certain of these viruses.

These studies are important for the entire field of cancer research, but are of special concern for vaccine safety. When an oncogenic virus is a contaminant of the vaccine, it can be eliminated by changing production techniques, but if the vaccine virus itself has an oncogenic potential, the problem is infinitely more complex. It takes many months of study involving large numbers of animals to determine the possible effects of such viruses.

DBS uses over 25,000 hamsters annually in its research and testing programs for oncogenicity.

Electron microscopy is also a valuable aid in searching for and identifying extraneous virus particles in cell cultures used in the production of vaccines.

BIOLOGICS STANDARDIZATION



Since most biological products cannot be standardized by chemical or physical means, their strength or potency must be tested in relation to established standards, or reference preparations.

The official physical standards for biological products in the United States, provided by law and regulations, are those established by the National Institutes of Health. To ensure that biological products made by several manufacturers will have uniform potency, the DBS provides manufacturers with these official standards. Their development depends on advanced knowledge in the fields of immunology, biology, virology, biochemistry, and medicine. More than 7,000 of the preparations prepared and tested are sent annually to manufacturers and others engaged in biologics standardization.

DBS scientists are constantly working to improve these preparations by developing more accurate and economical laboratory tests. For example, complex biological products are subjected to electrophoretic fractionation in order to identify the active components which will serve as more specific standards. DBS scientists are experimenting with stabilizers and freeze-drying techniques to develop better methods of preserving and storing biological products so that potency will be maintained. Studies are being carried out to establish standards of potency for new products pending licensing and for substances for which no suitable potency tests have been developed, such as allergenic products, poison ivy extracts, and certain bacterial vaccines.

There are compelling reasons why biological standards should be uniform throughout the world. This is best accomplished through international cooperation. DBS scientists serve on World Health Organization expert committees involved in the establishment of international standards, and assist other countries in establishing their own national standard preparations.

BLOOD RESEARCH AND CONTROL

Research in this field is designed to strengthen control procedures for the manufacture and storage of blood and blood derivatives.

During the past ten years, there has been a great increase in the use of such blood products as normal serum albumin, immune serum globulin, normal human plasma, frozen single-donor plasma for coagulation defects, and sera for determining blood groups and types, as well as whole blood for transfusions.

DBS scientists study the effects of freezing, thawing, and drying of these various elements of blood; the effect of storage conditions—temperature, time, light, and container materials—on the properties of whole plasma and the separate plasma proteins.

Of the estimated 5,000 blood banks in this country, 230 are operating under Federal license to ship human blood from one state to another for commercial use. These blood banks account for about 65 percent of the approximately 6,000,000 pints of blood collected annually. The remainder is collected by local blood banks for use within the community, and the medical procedures used are subject to local and state laws and regulations.

Blood banks licensed under the biological products control provisions of the Public Health Service Act must comply with standards set by DBS. To assure continued compliance with these standards, every licensed blood bank is inspected annually by DBS personnel, and tests are performed on random samples of blood selected by the inspectors.

INSPECTION

To ensure continued compliance with Public Health Service regulations, specially trained members of the DBS scientific staff annually inspect every establishment licensed to manufacture biologics, as well as those applying for license.

☆ U. S. GOVERNMENT PRINTING OFFICE : 1968 O - 284-418

There are more than 200 establishment licenses and over 1,300 product licenses in effect, covering approximately 290 specific products. These include:

Antitoxins
Immune serum globulins
Blood and blood derivatives
Bacterial vaccines
Toxoids
Toxins
Viral and rickettsial vaccines
Diagnostic substances for skin tests
Allergenic extracts
Antivenins
Poison ivy extracts
Venoms

photos: Roy Perry and
Jerry Hecht

THE NATIONAL INSTITUTES OF HEALTH
PUBLIC HEALTH SERVICE
U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service Publication No. 1744